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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MANNE SATYANARAYANA REDDY, SRINIVASAN THIRUMALAI RAJAN, UPPALA VENKATA BHASKARA RAO, and VADDADI PATTABHI RAMAYYA

Appeal 2012-000207
Application 10/601,844
Technology Center 1600

Before TONI R. SCHEINER, ERIC GRIMES, and STEPHEN WALSH, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to an antihistamine, which the Examiner has rejected for indefiniteness, anticipation, and obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part, but designate the affirmance a new ground of rejection.

STATEMENT OF THE CASE

"Cetirizine and its salts, including dihydrochloride, is known and is effective in the treatment of allergies. . . . Antihistamines, such as cetirizine,

block the effect of histamines." (Spec. 2.) "'[C]etirizine' is a generic term that denotes the racemic mixture of R and S enantiomers" (*id.* at 7). "The R enantiomer is referred to as levocetirizine" (*id.*). "Levocetirizine is believed to have a two-fold higher affinity for human H1 receptors than cetirizine. Levocetirizine is believed to be rapidly and extensively absorbed. Levocetirizine also has been shown to be free from side effects on the central nervous system." (*Id.* at 3.)

Claims 1-18 are on appeal. Claims 1 and 2 are representative and read as follows:

1. Amorphous levocetirizine dihydrochloride.

2. Amorphous levocetirizine dihydrochloride, which is substantially free of crystalline forms of cetirizine dihydrochloride.

The claims stand rejected as follows:

- Claims 2 and 10 under 35 U.S.C. § 112, second paragraph (Answer 4);
- Claims 1-16 under 35 U.S.C. § 102(b) as anticipated by each of Tang,[1] Pflum,[2] and Van de Venne[3] (Answer 5); and
- Claims 17 and 18 under 35 U.S.C. § 103(a) as obvious based on Van de Venne (Answer 8).

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[1] Tang Xiang-hong, et al., *Enantomeric Separation of Cetirizine Hydrochloride by HPLC*, 22(4) J. CHINA PHARM. UNIV. 311-312 (2002).
[2] Derek A. Pflum et al., *A Large-Scale Synthesis of Enantiomerically Pure Cetirizine Dihydrochloride Using Preparative Chiral HPLC,* 5 ORGANIC PROCESS RESEARCH & DEVLOP.110-115 (2001).
[3] Van de Venne et al., US 6,489,329 B2, Dec. 3, 2002.

I.

The Examiner has rejected claims 2 and 10 as indefinite, on the basis that "'substantially' . . . is a relative term, which renders the claim[s] indefinite. The term 'substantially' is not defined by the claim[s], the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." (Answer 4-5.)

Appellants argue that the Specification defines what is meant by "substantially free of crystalline forms," as recited in claims 2 and 10 (Appeal Br. 4, Reply Br. 6).

We agree with Appellants that the phrase "substantially free of crystalline forms" does not make claims 2 and 10 indefinite. The Specification states that "the term 'substantially free of crystalline forms of cetirizine dihydrochloride,' as used herein, means that the crystalline form of cetirizine dihydrochloride cannot be detected by methods known to those skilled in the art" (Spec. 7). The Examiner has not provided persuasive reasoning to support his conclusion that the use of "substantially" in this phrase renders claims 2 and 10 indefinite despite the Specification's express definition. The rejection under 35 U.S.C. § 112, second paragraph, is reversed.

II.

The Examiner has rejected claims 1-16 as anticipated by each of Tang and Van de Venne (Answer 5). The Examiner finds that "Tang teaches the levocetirizine dihydrochloride and falls within the range of Applicant's compounds" (*id.*) and that "Van de Venne teaches compositions comprising

levocetirizine dihydrochloride with one or more pharmaceutically acceptable excipients, and falls within the range of Applicant's compounds" (*id.* at 6).

The Examiner has also rejected claims 17 and 18 as obvious based on Van de Venne, because, although "[t]he claims differ from the reference by reciting the composition containing a moisture content . . . one skilled in the art would find the differences in the teaching to be negligible" (*id.* at 8).

Appellants argue that "[a]lthough the English portions of Tang apparently disclose an isolation of levocetirizine hydrochloride by high performance liquid chromatography, there is no teaching or suggestion that the isolated levocetirizine hydrochloride was in a solid form, or was amorphous" (Appeal Br. 4). Appellants also argue that while "Van de Venne . . . discloses compositions comprising levocetirizine dihydrochloride with one or more pharmaceutically acceptable excipients, . . . there is no teaching or suggestion that the levocetirizine dihydrochloride was amorphous" (*id.* at 5). Appellants argue that Van de Venne does not describe how its levocetirizine dihydrochloride was made, so it would be improper for the Examiner to shift the burden to them to show that it is not amorphous (Reply Br. 10).

We agree with Appellants that the Examiner has not provided an adequate basis for finding that Tang and Van de Venne disclosed amorphous levocetirizine dihydrochloride. As Appellants point out, Tang describes separation of the enantiomers of cetirizine dihydrochloride, but does not describe the separated enantiomers as amorphous, or even as solid.

Van de Venne discloses pharmaceutical compositions comprising "an effective amount of (i) pseudoephedrine . . . and an effective amount of (ii)

at least one compound selected from 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acid or amide derivatives" (Van de Venne, col. 2, l. 64 to col. 3, l. 1). "The most preferred compounds (ii) are the racemate . . known as cetirizine dihydrochloride, and its levorotatory and dextrorotatory enantiomers" (*id.* at col. 4, ll. 36-40).

Van de Venne discloses that its formulations can be in solid form (*id.* at col. 5, ll. 25-50) but, as Appellants point out, it does not describe them as amorphous or describe how the enantiomers of ceterizine dihydrochloride are isolated. The reference therefore provides insufficient evidence to support the Examiner's conclusion (Answer 6) that it inherently discloses the claimed amorphous levocetirizine dihydrochloride.

We reverse the rejection of claims 1-16 as anticipated by either Tang or Van de Venne. Because the Examiner's obviousness rejection (Answer 8) is addressed only to the moisture content limitations of claims 17 and 18, we also reverse the rejection of claims 17 and 18 as obvious based on Van de Venne.

III.

Issue

The Examiner has rejected claims 1-16 as anticipated by Pflum, on the basis that Pflum inherently discloses the amorphous form of levocetirizine dihydrochloride (Answer 5-7). The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii).

Appellants contend that Pflum "does not teach or suggest that the resulting levocetirizine dihydrochloride was amorphous" (Appeal Br. 5).

The issue with respect to this rejection is: Does the evidence provide an adequate basis for shifting the burden to Appellants to show that Pflum's levocetirizine dihydrochloride was *not* amorphous?

Findings of Fact

1. Pflum discloses enantiomerically pure ceterizine dihydrochloride (Pflum 110, title).

2. Pflum refers to racemic cetirizine dihydrochloride as "(±)-**1**" (*id.* at 110, Fig. 1).

3. Pflum describes a process of making the (R) form of compound **1**; i.e., the R form of cetirizine dihydrochloride, or levocetirizine dihydrochloride (*id.* at 114, right col., last full ¶; Spec. 7).

4. Pflum states that HCl was added to a solution of a precursor compound ("(R)-**2**"), then

> the reaction mixture was distilled to remove the methanol as it formed. The organic phase was removed, and to the aqueous phase was added methyl ethyl ketone (MEK, 70 L total). Azeotropic removal of water . . . provided a slurry of (R)-**1** in MEK which was filtered, washed with MEK (5.5 kg), and dried to furnish the title compound (1.2 kg, 74%) with >99% purity.

(Pflum 114, right col., last full ¶.)

5. The Specification exemplifies the following method of making amorphous levocetirizine dihydrochloride:

> Levocetirizine dihydrochloride (10.0 grams) was dissolved in a mixture of acetone (40 ml) and water (100 ml). The reaction mixture was stirred at a temperature of 25-35°C to get a clear solution. The reaction solution was then filtered and the solvent was completely distilled off from the reaction solution to dryness . . . to result [in] the amorphous form of levocetirizine dihydrochloride.

(Spec. 16 (Example 4).)

Principles of Law

> Where . . . the claimed and prior art products are identical or substantially identical . . . the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . [The] fairness [of the burden-shifting] is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

In re Best, 562 F.2d 1252, 1255 (CCPA 1977).

"[W]hen the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).

Analysis

Claim 1 is directed to "[a]morphous levocetirizine dihydrochloride" and therefore reads on any amount of levocetirizine dihydrochloride, in the amorphous form. *See SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1339 (Fed. Cir. 2005) (claim to crystalline paroxetine hydrochloride hemihydrate "encompasses, without limitation, PHC hemihydrate – a crystal form of paroxetine hydrochloride that contains one molecule of bound water for every two molecules of paroxetine hydrochloride in the crystal structure").

Pflum discloses a method of making solid levocetirizine dihydrochloride that is very similar to the method described in the Specification's Example 4. Both methods include a solution of levocetirizine dihydrochloride in a mixture of water and a ketone solvent – Pflum's because the levocetirizine dihydrochloride results from conversion of the corresponding

methyl ester ("(R)-**2**") and the Specification's because levocetirizine dihydrochloride was directly dissolved in the mixed solvents. In Pflum's method the water is removed to provide a slurry of (precipitated) levocetirizine dihydrochloride, which is then filtered out of the remaining solvent and dried, while in the Specification's method the solvent is distilled off completely to yield dried levocetirizine dihydrochloride. Both methods, therefore, separate the solid levocetirizine dihydrochloride from the solvent mixture.

In addition, it is noteworthy that Pflum does not characterize its (R)-**1** product as crystalline but does characterize another product as "crystallized" (*compare* Pflum 114, right col., middle and last full ¶¶). The fact that Pflum noted the crystalline nature of some products, but not its (R)-**1** product, provides further evidence that the solid (R)-**1** was not crystalline, and therefore amorphous. *Cf.* Spec. 3-4 (distinguishing between the amorphous form of a drug and crystalline forms).

We conclude that the similarity between Pflum's method of making levocetirizine dihydrochloride and the Specification's Example 4, describing a method of making amorphous levocetirizine dihydrochloride, provides an adequate basis for concluding that Pflum disclosed amorphous levocetirizine dihydrochloride even though it did not characterize it as such. Pflum's characterization of some products, but not (R)-**1**, as crystalline supports this conclusion. Thus, the burden is properly shifted to Appellants to provide evidence that carrying out the process disclosed by Pflum does not result in amorphous levocetirizine dihydrochloride.

Conclusion of Law

The evidence provides an adequate basis for shifting the burden to Appellants to show that Pflum's levocetirizine dihydrochloride was *not* amorphous.

SUMMARY

We reverse the rejection under 35 U.S.C. § 112, second paragraph, and the prior art rejections based on Tang and Van de Venne.

We affirm the rejection of claims 1-16 as anticipated by Pflum. However, since our reasoning differs significantly from the Examiner's, we designate the affirmance a new ground of rejection to give Appellants a fair opportunity to respond to the reasoning that we rely on.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 CFR § 41.50(b) also provides that the appellants, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .

(2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

AFFIRMED-IN-PART, 37 C.F.R. § 41.50(b)

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